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Long term outcomes of drug-eluting stent versus coronary artery bypass grafting for left main coronary artery disease: a meta-analysis

Kong-Yong CUI[1], Shu-Zheng LYU[1], Xian-Tao SONG[1], Fei YUAN[1], Feng XU[1], Min ZHANG[1], Ming-Duo ZHANG[1], Wei WANG[1], Dong-Feng ZHANG[1], Jing DAI[1], Jin-Fan TIAN[1], Yun-Lu WANG[2]

[1]*Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China*
[2]*Department of Anesthesiology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China*

Abstract

Background It is still controversial whether percutaneous coronary intervention with drug-eluting stent (DES) is safe and effective compared to coronary artery bypass graft surgery (CABG) for unprotected left main coronary artery (ULMCA) disease at long-term follow up (≥ 3 years). **Methods** Eligible studies were selected by searching PubMed, EMBASE, and Cochrane Library up to December 6, 2016. The primary endpoint was a composite of death, myocardial infarction (MI) or stroke during the longest follow-up. Death, cardiac death, MI, stroke and repeat revascularization were the secondary outcomes. **Results** Four randomized controlled trials and twelve adjusted observational studies involving 14,130 patients were included. DES was comparable to CABG regarding the occurrence of the primary endpoint (HR = 0.94, 95% CI: 0.86–1.03). Besides, DES was significantly associated with higher incidence of MI (HR = 1.56, 95% CI: 1.09–2.22) and repeat revascularization (HR = 3.09, 95% CI: 2.33–4.10) compared with CABG, while no difference was found between the two strategies regard as the rate of death, cardiac death and stroke. Furthermore, DES can reduce the risk of the composite endpoint of death, MI or stroke (HR = 0.80, 95% CI: 0.67–0.95) for ULMCA lesions with SYNTAX score ≤ 32. **Conclusions** Although with higher risk of repeat revascularization, PCI with DES appears to be as safe as CABG for ULMCA disease at long-term follow up. In addition, treatment with DES could be an alternative interventional strategy to CABG for ULMCA lesions with low to intermediate anatomic complexity.

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Keywords: Coronary artery bypass graft; Drug-eluting stent; Long term; Unprotected left main coronary disease

1 Introduction

Significant unprotected left main coronary artery (ULMCA) disease occurs in 5%–7% of patients undergoing coronary angiography.[1,2] For several decades, coronary artery bypass graft surgery (CABG) has been recommended as the standard treatment for ULMCA disease owing to its survival benefit over medical therapy.[1,2] At the same time, the adaptation of drug-eluting stent (DES) in percutaneous coronary intervention (PCI) has led to a significant reduction in the risk of restenosis and repeat revascularization in comparison with bare-metal stent (BMS).[3,4] With the improvement of stent design, procedural technique and adjunctive medical therapy, PCI with DES is increasingly considered as a safe and feasible approach for patients with ULMCA disease.

Previous studies suggested the incidence of long-term death and overall safety endpoint of death, myocardial infarction (MI) or stroke were comparable between PCI and CABG for ULMCA disease.[5–7] In the current guidelines, PCI receives a class I or IIa recommendation for patients with low SYNTAX score, while a class IIa or IIb recommendation for patients with intermediate anatomic complexity.[1,2] Obviously, PCI with DES can be a viable alternative to CABG for ULMCA disease, especially in patients with low to intermediate anatomic complexity.

However, previous meta-analyses had a limited follow-up duration of ≤ 3 years, while the most recent meta-analysis concentrating on long-term outcomes comparing DES and CABG was restricted to a small sample size and studies using mixtures of BMS and DES were enrolled.[7,8] Recently, the EXCEL trial indicates that PCI with everolimus-eluting stents is noninferior to CABG with respect to the overall

Correspondence to: Shu-Zheng LYU, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart, Lung and Blood Vessel Diseases, 2 Anzhen Road, Beijing 100029, China. E-mail: shuzheng@medmail.com.cn

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combined incidence of death, myocardial infarction (MI) or stroke at three years,[9] while the NOBLE study suggests CABG may be better than biolimus-eluting stent regarding lower rate of 5-year major adverse cardiac or cerebrovascular events (MACCE).[10] Unfortunately, it is still controversial whether DES is safe and effective compared to CABG for ULMCA disease at long-term follow up. We performed a meta-analysis including only trials with a follow-up duration of at least three years to examine the long-term relative safety and efficacy of DES and CABG for ULMCA lesions.

2 Methods

2.1 Search strategy

A comprehensive search of electronic database in PubMed, EMBASE, and Cochrane Library up to December 6, 2016 was performed to identify the pertinent articles regarding DES versus CABG for ULMCA disease. The following medical subject headings and search terms were used: "percutaneous coronary intervention", "PCI", "stent", "drug-eluting stent", "DES", "coronary artery bypass", and "left main". The references of the identified articles and relevant reviews were screened to include other potentially suitable trials.

2.2 Study selection

Studies satisfying the following criteria were eligible: (1) randomized controlled trials (RCTs) or adjusted observational studies (propensity-score matching > propensity-score adjusted > multivariable adjusted) regarding ULMCA disease; (2) compared DES to CABG; (3) followed for ≥ 3 years. Studies were excluded if they met any one of the following criteria: (1) not published in English; (2) published as an abstract or conference proceedings; (3) with the same patient sample; (4) using BMS exclusively or mixtures of BMS and DES without outcomes comparing DES with CABG separately. When several reports overlapped with each other, we selected the largest and the latest study. Two independent investigators (MDZ and WW) reviewed the studies to determine whether they met the inclusion criteria and any disagreement was resolved by consensus.

2.3 Data extraction

The following data was independently extracted by two authors (FX and MZ) through a standardized form: study characteristics, patient characteristics, and clinical outcomes. Hazard ratios (HR) of the time-to-event outcomes or odds ratios (OR) calculated from dichotomous outcomes were extracted. The primary endpoint was a composite of death, MI or stroke during the longest follow-up. Death, cardiac death, MI, stroke and repeat revascularization were the secondary outcomes, and they were defined variable in each study (Table 1S).

2.4 Quality assessment

The RCTs were evaluated by following the methodological criteria recommended by the Cochrane Collaboration: sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias,[11] whereas the observational studies were evaluated by the Newcastle-Ottawa Scale criteria.[12]

2.5 Statistical analysis

Quantitative analysis with the generic inverse variance random-effect model was performed to estimate the pooled HRs or ORs with their 95% confidence internals (CIs). Potential heterogeneity among studies was quantified with I^2 and a value of > 50% was defined as statistical heterogeneity. Furthermore, we used funnel plots to assess the potential publication bias.

Subgroup analysis was carried out to explore the sources of heterogeneity according to the study design (RCTs or adjusted observational studies). Additionally, sensitivity analysis was conducted by performing a separate analysis according to the following variables: (1) duration of follow up ≥ 5 years; (2) SYNTAX score ≤ 32 or > 32. To demonstrate the robustness of the results, we investigated the influence of a single study on the overall effect by omitting one study in each turn. All *P* values were two-sided, and results were considered statistically significant at $P < 0.05$.

This study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[13] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist.[14] All statistical analysis was performed with Review Manager 5.1 (Cochrane Center, Denmark).

3 Results

3.1 Eligible studies

After a comprehensive search, 2103 potentially relevant articles were identified in the initial analysis. One hundred and nineteen articles were chosen for complete review, and finally, 16 studies were included in the present meta-analysis.[9,10,15–28] The process of selecting studies for the meta-analysis is briefly depicted in Figure 1 and the methodology as well as the population characteristics are presented in Table 1.

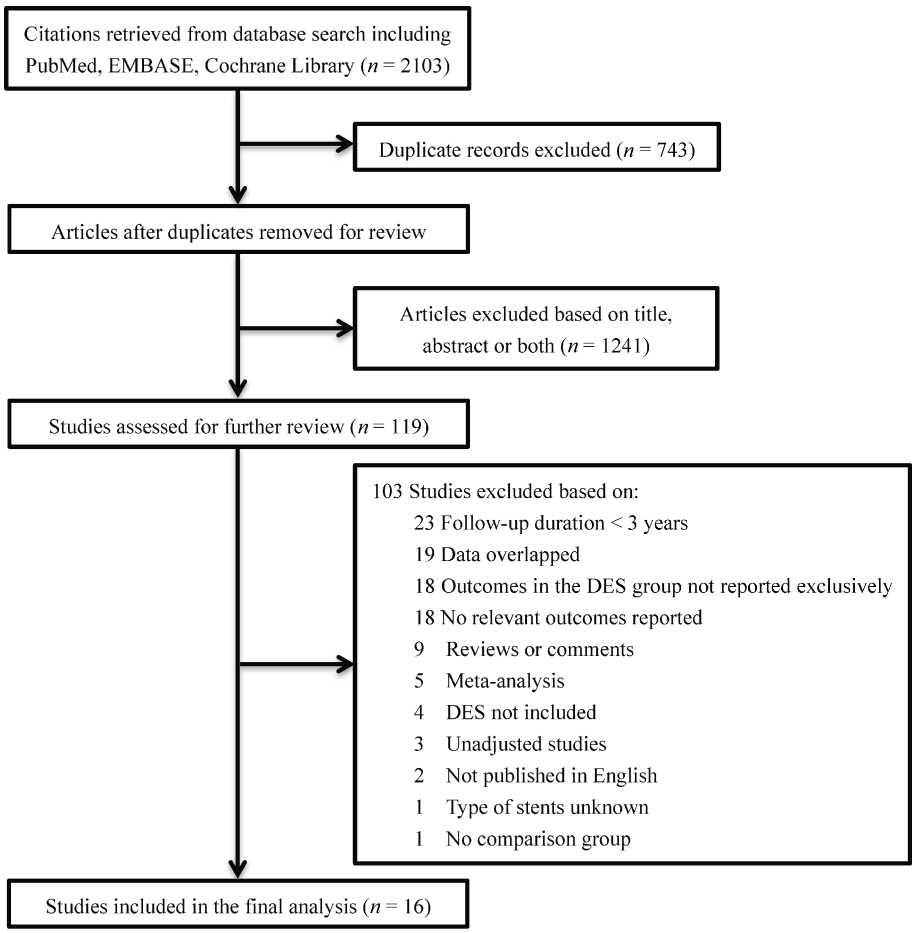

Figure 1. Process for study selection.

Among the 16 trials (four RCTs, six propensity-score matching studies, and six propensity-score adjusted studies), 6333 and 7797 patients were treated with DES and CABG, respectively. Odds ratios were reported or calculated in two studies from dichotomous outcomes provided at five year follow-up.[17,26] Eligible studies were published between 2009 and 2016, while the clinical follow-up period ranged from 3 to 8 years. Quality assessment results are described in Table 2S and Table 3S. The funnel plot of the primary endpoint indicates that no publication bias was found (Figure 1S). Overall, intravascular ultrasound (IVUS) guided PCI was performed in 56.1% of the patients. Additionally, 47.6% of the patients underwent CABG with off-pump technique, while a left anterior internal mammary artery graft was used in 92.5% of the patients who received CABG (Table 1).

3.2 Primary endpoint

In summary, the composite of death, MI or stroke was reported in 13 studies. Treatment with DES was comparable to that of CABG regarding the incidence of a composite of death, MI or stroke without heterogeneity for ULMCA disease (HR = 0.94, 95% CI: 0.86–1.03, P = 0.20, I^2 = 0) (Figure 2).

3.3 Secondary endpoints

There was no significant difference in the incidence of all-cause death (HR = 1.11; 95% CI: 0.92–1.32, P = 0.28) (Figure 3) as well as the risk of cardiac death (HR = 1.13, 95% CI: 0.75–1.72, P = 0.55) (Figure 4) between the two strategies. Nevertheless, signs of statistical heterogeneity regarding cardiac death were found across trials (I^2 = 73%). Subgroup analysis by excluding observational studies showed the rate of cardiac death was comparable between the two groups without statistical heterogeneity (HR = 1.00, 95% CI: 0.72–1.39, P = 0.99, I^2 = 21%).

Overall, the risk of MI was significantly higher in the DES group in comparison with the CABG group (HR = 1.56, 95% CI: 1.09–2.22, P = 0.01, I^2 = 69%) (Figure 5). Subgroup analysis showed treatment with DES was associated with increased risk of MI in observational studies (HR = 1.67, 95% CI: 1.05–2.63, P = 0.03, I^2 = 56%), whereas no significant difference was found between the two groups in RCTs (HR = 1.48; 95% CI: 0.85–2.58, P = 0.17, I^2 = 67%).

Table 1. The methodology and the population characteristics of studies.

Study	No. patients*	Study design	Adjusted method	Study period	Follow up, yrs	Type of DES	Off-pump procedure, %	LIMA-LAD graft, %	Complete artery grafting, %	Guidance with IVUS, %
ASAN-MAIN 2010[15]	176/219	Retrospective, multicenter	Propensity-score adjusted	2003.1–2004.5	5	PES 4.5%, SES 95.5%	18.7	95.4	NA	89.2
Chang 2012[16]	190/190	Observational, multicenter	Propensity-score matching	2003.5–2009.12	4	NA	NA	NA	NA	NA
Chieffo 2010[17]	107/142	Retrospective, single center	Propensity-score adjusted	2002.3–2004.7	5	PES 48.6%, SES 51.4%	39.5	NA	NA	28.9
DELTA 2012[18]	602/602	Retrospective, multicenter	Propensity-score matching	2002.4–2006.4	3	PES 47.7%, SES 47.7%, second-generation DES 4.6%	NA	NA	NA	NA
EXCEL 2016[9]	948/957	RCT, multicenter	Not needed	2010.9–2014.3	3	EES	29.4	98.8	24.8	77.2
Gao 2016[19]	236/354	Retrospective, single center	Propensity-score adjusted	2008.3–2010.12	3	NA	NA	NA	NA	NA
Jeong 2013[20]	159/159	Retrospective, single center	Propensity-score matching	2001.1–2009.12	8	NA	100	100	90	NA
Kang 2010[21]	104/104	Retrospective, two centers	Propensity-score matching	2003.1–2006.12	3	PES 26.3%, SES 70.2%, ZES 3.4%	NA	NA	NA	NA
MAIN-COMPARE 2010[22]	396/396	Observational, multicenter	Propensity-score matching	2003.5–2006.6	5	NA	NA	NA	NA	NA
NOBLE 2016[10]	592/592	RCT, multicenter	Not needed	2008.12–2015.1	5	First-generation DES 11%, BES 89%	15.6	93.4	94.1	46.8
PRECOMBAT 2015[23]	300/300	RCT, multicenter	Not needed	2004.4–2009.8	5	SES	63.8	93.6	NA	91.2
SYNTAX 2014[24]	357/348	RCT, multicenter	Not needed	2005.3–2007.4	5	PES	NA	NA	NA	NA
Wu 2010[25]	131/245	Retrospective, single center	Propensity-score adjusted	2003.2–2006.12	4	SES 96.2%, ZES 3.8%	22	NA	NA	NA
Yi 2012[26]	128/128	Retrospective, single center	Propensity-score matching	2003.7–2007.6	5	NA	100	NA	NA	NA
Yu 2016[27]	465/457	Retrospective, single center	Propensity-score adjusted	2003.1–2009.7	7	NA	92.3	85.3	NA	NA
Zheng 2016[28]	1442/2604	Prospective, single center	Propensity-score adjusted	2004.1–2010.12	3	NA	53.3	94.2	NA	38.8
Summary	NA	NA	NA	NA	NA	NA	47.6	92.5	53.6	56.1

*The numerals indicate the numbers of patients in the DES group and the CABG group, respectively. ASAN-MAIN: ASAN medical center-left main revascularization; BES: biolimus-eluting stent; CABG: coronary artery bypass grafting; DELTA: drug-eluting stent for left main coronary artery disease; DES: drug-eluting stent; EES: everolimus-eluting stent; EXCEL: evaluation of Xience versus coronary artery bypass surgery for effectiveness of left main revascularization; IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LIMA: left internal mammary artery; MAIN-COMPARE: revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization study; NA: not applicable; NOBAL: Nordic-Baltic-British left main revascularization; PES: paclitaxel-eluting stent; PRECOMBAT: premier of randomized comparison of bypass surgery versus angioplasty using sirolimus-eluting stent in patients with left main coronary artery disease; RCT: randomized controlled trial; SES: sirolimus-eluting stent; SYNTAX: synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; ZES: zotarolimus-eluting stent.

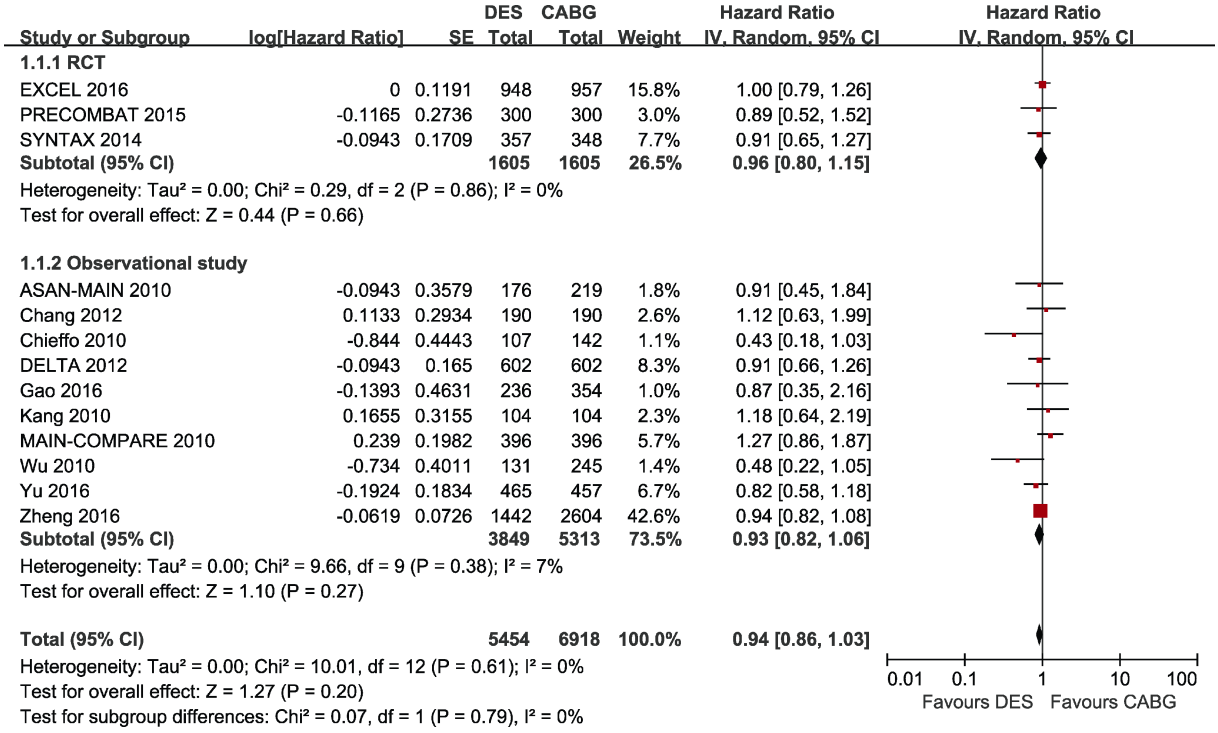

Figure 2. Forest plot of the composite of death, myocardial infarction or stroke. CABG: coronary artery bypass graft surgery; DES: drug-eluting stent.

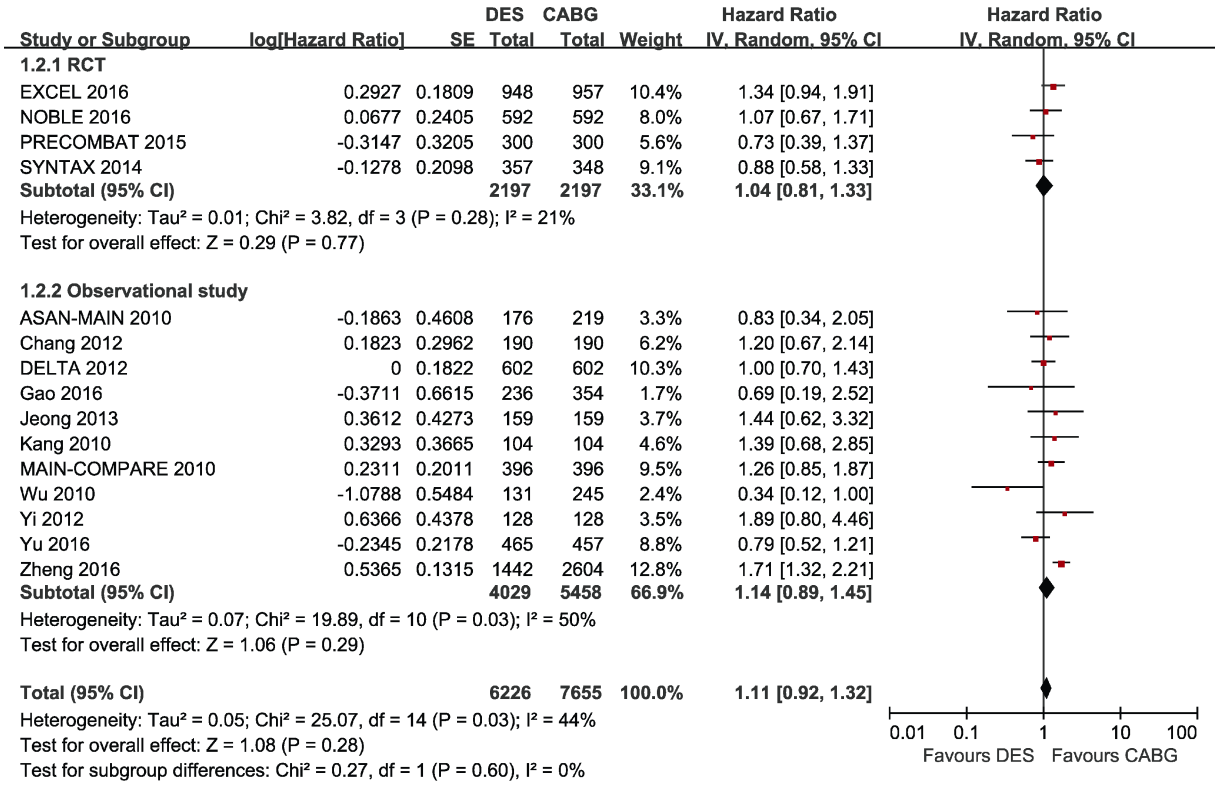

Figure 3. Forest plot of all-cause death. CABG: coronary artery bypass graft surgery; DES: drug-eluting stent.

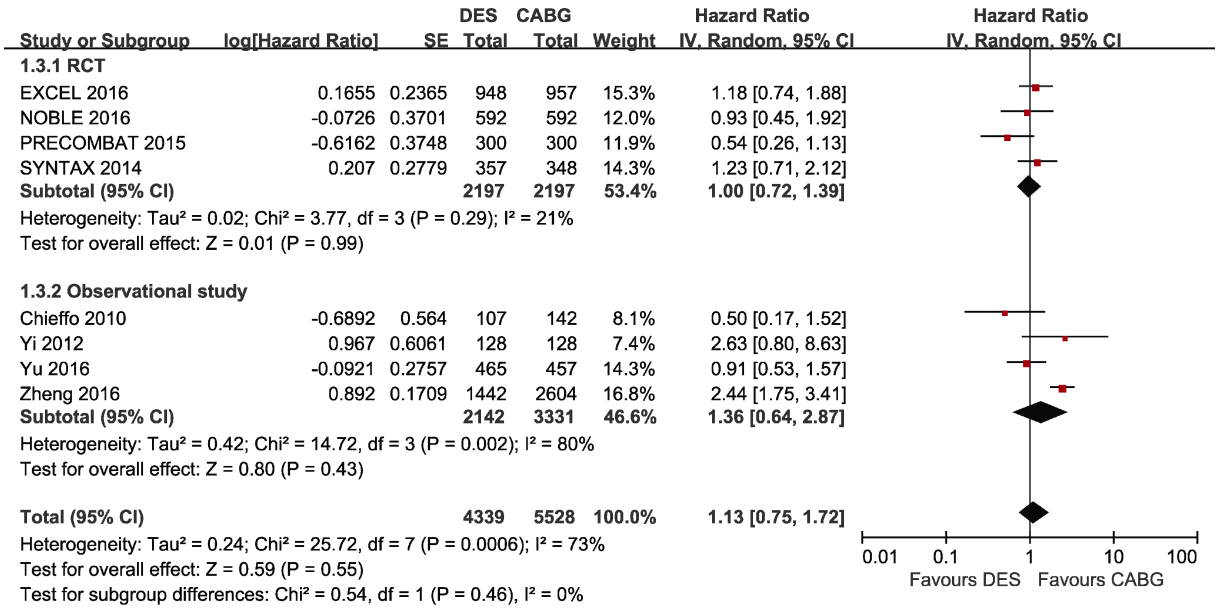

Figure 4. Forest plot of cardiac death. CABG: coronary artery bypass graft surgery; DES: drug-eluting stent.

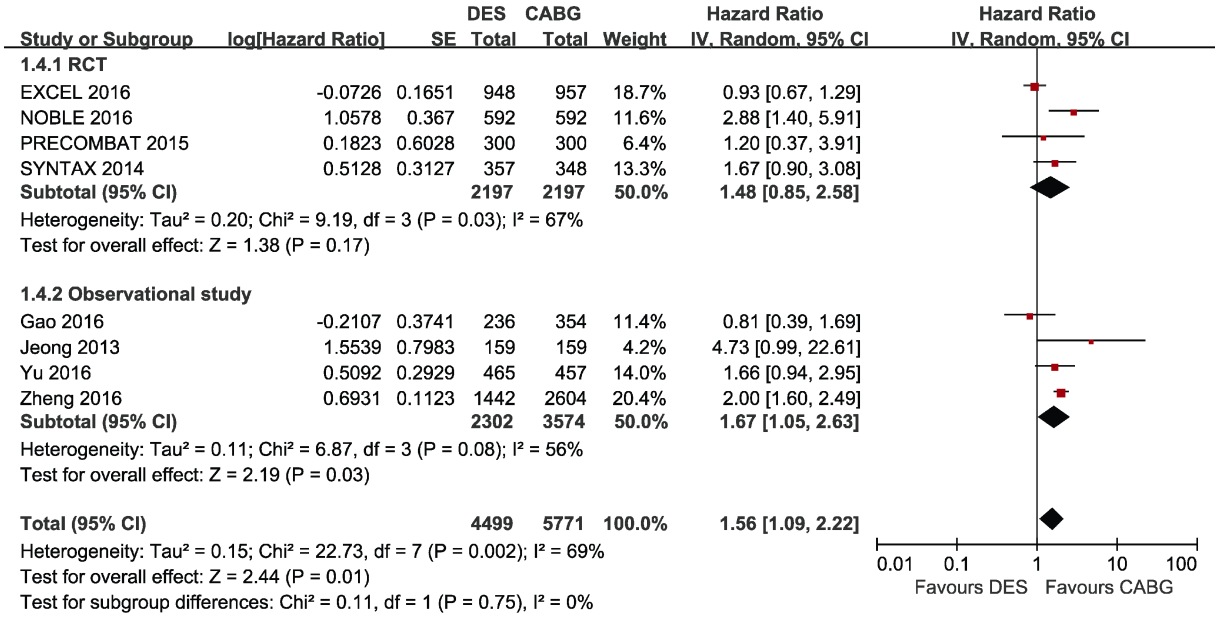

Figure 5. Forest plot of myocardial infarction. CABG: coronary artery bypass graft surgery; DES: drug-eluting stent.

In the pooled estimate, the risk of stroke was not significantly different between the two treatment strategies with statistical heterogeneity (HR = 0.61, 95% CI: 0.29–1.29, P = 0.20, I^2 = 84%) (Figure 6). However, CABG was inferior to DES in terms of higher rate of stroke in observational studies (HR = 0.39, 95% CI: 0.17–0.91, P = 0.03, I^2 = 73%).

The data in Figure 7 indicated that the pooled HR of DES for repeat revascularization was significantly higher in the overall analysis (HR = 3.09, 95% CI: 2.33–4.10, P < 0.00001, I^2 = 79%), RCTs (HR = 1.70, 95% CI: 1.42–2.05, P < 0.00001, I^2 = 0) and observational studies (HR = 3.92, 95% CI: 3.05–5.04, P < 0.00001, I^2 = 48%).

3.4 Sensitivity analysis

Sensitivity analyses conducted through the removal of any single trial showed that it did not essentially affect the overall pooled estimate. Furthermore, when the study by Zheng, *et al*.[28] was removed, no statistical heterogeneity

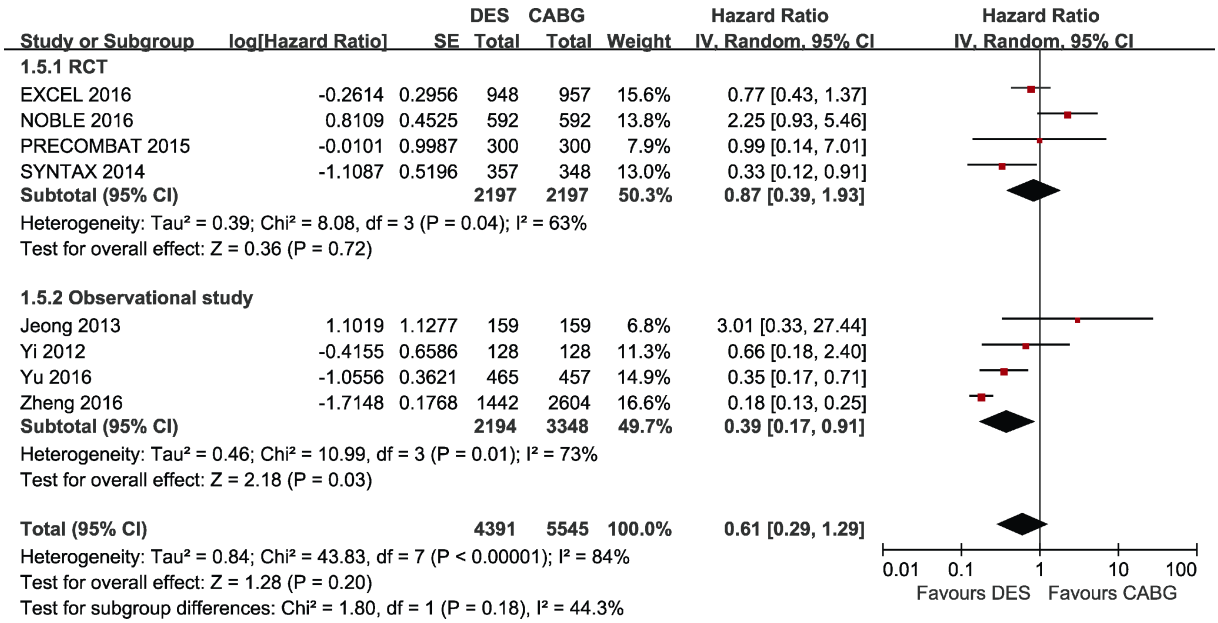

Figure 6. Forest plot of stroke. CABG: coronary artery bypass graft surgery; DES: drug-eluting stent.

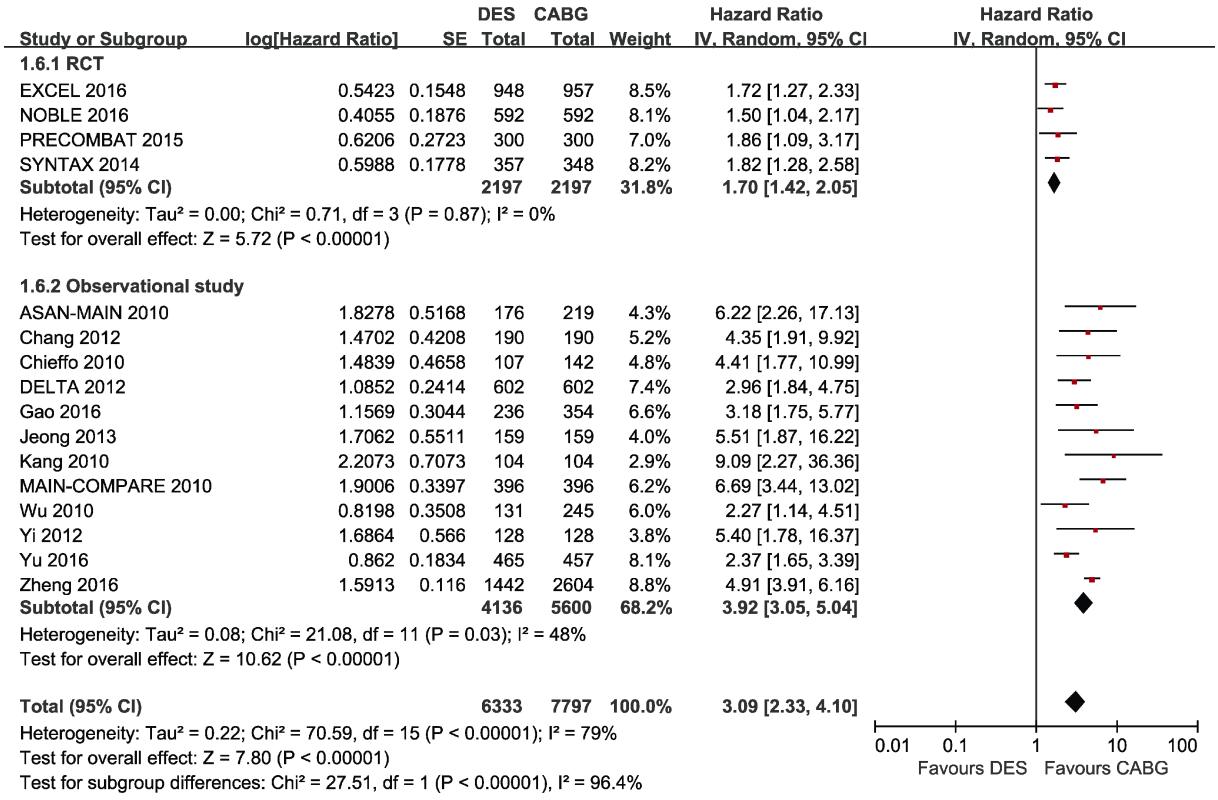

Figure 7. Forest plot of repeat revascularization. CABG: coronary artery bypass graft surgery; DES: drug-eluting stent.

was found regarding cardiac death (HR = 0.99, 95% CI: 0.74–1.32, $P = 0.92$, $I^2 = 24\%$) (Data not shown), while statistical heterogeneity was not existed any more by excluding the EXCEL study[9] in terms of MI (HR = 1.78, 95% CI: 1.33–2.37, $P < 0.0001$, $I^2 = 33\%$) (Data not shown).

Besides, sensitivity analyses according to the follow-up

duration (≥ 5 years) obtained mostly similar results compared to the overall analysis. Analysis after excluding the trials with follow-up duration < 5 years showed DES was associated with higher rate of MI compared with CABG without heterogeneity (HR= 1.92, 95% CI: 1.37–2.69, P = 0.0002, I^2 = 0) (Figure S2).

In patients with SYNTAX score ≤ 32, DES was superior to CABG in terms of the composite of death, MI or stroke (HR = 0.80, 95% CI: 0.67–0.95, P = 0.01, I^2 = 0). Nevertheless, treatment with DES was inferior to CABG regarding the primary endpoint (HR = 1.45, 95% CI: 1.06–1.97, P = 0.02, I^2 = 42%) in patients with SYNTAX score > 32 (Figure S3).

4 Discussion

The present meta-analysis with approximately 15,000 patients comparing the long-term safety and efficacy between DES and CABG for ULMCA disease demonstrated that: (1) PCI with DES was comparable to CABG regarding the rate of the primary endpoint compositing death, MI or stroke; (2) The incidence of MI and repeat revascularization were higher in the DES group compared with the CABG group, while no significant difference was found between the two treatment strategies regard as the risk of death, cardiac death and stroke; and (3) DES might be a safe and effective alternative to CABG for ULMCA disease with low to intermediate anatomic complexity.

Studies with small sample size demonstrated that no difference for the safety endpoint compositing death, MI or stroke between the two strategies for patients with ULMCA lesions.[7,8] Nevertheless, one study mixed BMS in the PCI group,[7] while the other enrolled study with outcomes at only 1 year follow-up,[8] therefore severe heterogeneity could not be avoided under the circumstances. In our study, the occurrence of the primary endpoint composite of death, MI or stroke in the DES group was comparable to the CABG group without heterogeneity.

All-cause mortality remained similar between the two strategies, which was in accordance with the studies with short-term data[5,6] and meta-analyses with long-term follow up.[7,8] Furthermore, we found that there was no difference between the two strategies regard as long-term cardiac mortality which was not reported in prior studies.

Previous meta-analyses concluded that the risk of MI was comparable between the two revascularization approaches,[5,7,8] whereas Athappan, *et al*.[6] reported that there was a trend in favor of CABG regard as the lower risk of MI at 1 year, 2 years and 3 years. Although with statistical heterogeneity, the occurrence of long-term MI also showed a trend towards a lower risk in patients received CAGB in the present study. Nonetheless, the result should be interpreted with caution as no difference was found in RCTs. The predominantly used first-generation DES and the insufficiency antiplatelet therapies may have contributed to this finding. Recently, Palmerini, *et al*.[29] has demonstrated that newer-generation DES, especially cobalt-chromium everolimus-eluting stents, can reduce stent thrombosis as well as MI in comparison with first-generation DES. Therefore, the introduction of newer-generation DES and more potent antiplatelet therapies will likely reduce the occurrence of MI for patients received PCI.

In the current study, the long-term risk of stroke was reported to be comparable between the two groups which was consistent with other studies.[7,8] Nonetheless, the rate of stroke in the CABG group was reported to be significantly more frequent in adjusted observational studies. Notably, off-pump CABG could reduce the incidence of adverse neurological sequelae in contrast with cardiopulmonary bypass.[30] In addition, the lower incidence of dual antiplatelet therapy after revascularization with CABG might have resulted in this result. Overall, off-pump technique and dual antiplatelet therapy should be applied to reduce the risk of stroke for patients received CABG.

Over the past few years, CABG has improved the outcomes by the adaption of off-pump technique and arterial grafting. The internal mammary arteries have been widely used as the conduit to the left anterior descending coronary artery due to its long-term patency.[31] Interestingly, 92.5% of patients received a left internal mammary artery to left anterior descending coronary artery graft and complete artery grafting was performed in 53.6% of patients treated with CABG in our meta-analysis. Furthermore, the left internal mammary artery clearly exhibited less downstream coronary disease progression in the left anterior descending coronary artery compared with DES.[32]

First-generation DES was used in most of the studies, while it has been postulated that newer-generation DES with novel stent materials, platforms, as well as more biocompatible polymers could reduce the incidence of revascularization.[33] With the development of the stent design, the gap will be narrowed between the two strategies. Furthermore, it should be noted that routine angiographic follow-up was performed to detect early left main in-stent restenosis rather than clinically driven in most of the studies, which may cause higher rate of revascularization in the DES group. For patients treated with CABG, clinical symptoms

may not occur with graft occlusion if the blood to left ventricle myocardium was partly supplied through the native vessel, which may underestimate the repeat revascularization discrepancy.

IVUS plays an important role in assessing lesion severity, selecting treatment strategy, optimizing stent implantation and subsequently obtaining better clinical and angiographic results.[34] Furthermore, previous studies have demonstrated intravascular ultrasound-guided DES implantation is associated with a greater benefit in patients with complex lesions such as bifurcations and ULMCA disease[35] in that it supplies beneficial effect on stent expansion in complex settings. Although optical coherence tomography with high resolution has emerged as an alternative imaging modality in suitable patients, it is challenging to create a blood-free environment for clear image especially in the left main ostium.[36] Fractional flow reserve is a well-established adjunct for assessing the physiological significance of stenosis. In clinical scenarios, these new interventional techniques should be given a full consideration when performing PCI with DES in ULMCA lesions.

Our meta-analysis presents a number of limitations that cannot be ignored. First, this study included both, RCTs and adjusted observational studies which can introduce a potential bias. Second, the definition of clinical endpoints slightly differed across the individual trials, although no signs of heterogeneity were observed for the primary endpoint. In fact, stratified analysis limited to more homogeneous subgroups of patients was performed and random effects model was used to account for the heterogeneity. Third, the duration of follow-up across trials was variable, and subset analysis (≥ 5 years) was performed. Fourth, different types of DES in the various trials had become an important source of heterogeneity. Although first-generation DES was predominantly applied, newer-generation DES was used in some lesions. Among the CABG strategies, the rates of left internal mammary artery to left anterior descending coronary artery graft adaption, complete artery grafting and cardiopulmonary bypass adaption were different across the studies. Fifth, subset analyses to evaluate the effect of SYNTAX score on clinical endpoints were performed in our study. Nevertheless, available data was scarce and incomplete reporting may result in underpowered analyses for certain outcomes.

In conclusion, the current meta-analysis shows that treatment with DES appears to be as safe as CABG for ULMCA disease at long-term follow up, although with higher risk of repeat revascularization. In addition, PCI with DES could be an alternative interventional strategy to CABG for ULMCA lesions with low to intermediate anatomic complexity. More large-scale RCTs with long-term outcomes are needed.

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References

1 Windecker S, Kolh P, Alfonso F, *et al*. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; 35: 2541–2619.

2 Fihn SD, Gardin JM, Abrams J, *et al*. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012; 60: e44–e164.

3 Kim YH, Park DW, Lee SW, *et al*. Long-term safety and effectiveness of unprotected left main coronary stenting with drug-eluting stents compared with bare-metal stents. *Circulation* 2009; 120: 400–407.

4 Fokkema ML, James SK, Albertsson P, *et al*. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J Am Coll Cardiol* 2013; 61: 1222–1230.

5 Capodanno D, Stone GW, Morice MC, *et al.* Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. *J Am Coll Cardiol* 2011; 58: 1426–1432.

6 Athappan G, Patvardhan E, Tuzcu ME, *et al.* Left main coronary artery stenosis: a meta-analysis of drug-eluting stents versus coronary artery bypass grafting. *JACC Cardiovasc Interv* 2013; 6: 1219–1230.

7 Gargiulo G, Tamburino C, Capodanno D. Five-year outcomes of percutaneous coronary intervention versus coronary artery bypass graft surgery in patients with left main coronary artery

disease: An updated meta-analysis of randomized trials and adjusted observational studies. *Int J Cardiol* 2015; 195: 79–81.

8 Nerlekar N, Ha FJ, Verma KP, *et al.* Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery stenosis: a meta-analysis of randomized trials. *Circ Cardiovasc Interv* 2016; 9: e004729.

9 Stone GW, Sabik JF, Serruys PW, *et al*. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med* 2016; 375: 2223–2235.

10 Makikallio T, Holm NR, Lindsay M, *et al*. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet* 2016; 388: 2743–2752.

11 Lundh A, Gotzsche PC. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. *BMC Med Res Methodol* 2008; 8: 22.

12 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603–605.

13 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.

14 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000; 283: 2008–2012.

15 Park DW, Kim YH, Yun SC, *et al*. Long-term outcomes after stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 10-year results of bare-metal stents and 5-year results of drug-eluting stents from the ASAN-MAIN (ASAN Medical Center-Left MAIN Revascularization) Registry. *J Am Coll Cardiol* 2010; 56: 1366–1375.

16 Chang K, Koh YS, Jeong SH, *et al*. Long-term outcomes of percutaneous coronary intervention versus coronary artery bypass grafting for unprotected left main coronary bifurcation disease in the drug-eluting stent era. *Heart* 2012; 98: 799–805.

17 Chieffo A, Magni V, Latib A, *et al*. 5-year outcomes following percutaneous coronary intervention with drug-eluting stent implantation versus coronary artery bypass graft for unprotected left main coronary artery lesions the Milan experience. *JACC Cardiovasc Interv* 2010; 3: 595–601.

18 Chieffo A, Meliga E, Latib A, *et al*. Drug-eluting stent for left main coronary artery disease. The DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv* 2012; 5: 718–727.

19 Gao F, Zhou YJ, Wang ZJ, *et al.* Transradial coronary intervention versus coronary artery bypass grafting for unprotected left main and/or multivessel disease in patients with acute coronary syndrome. *Angiology* 2016; 67: 83–88.

20 Jeong DS, Lee YT, Chung SR, *et al.* Revascularization in left main coronary artery disease: comparison of off-pump coronary artery bypass grafting vs percutaneous coronary intervention. *Eur J Cardiothorac Surg* 2013; 44: 718–724.

21 Kang SH, Park KH, Choi DJ, *et al.* Coronary artery bypass grafting versus drug-eluting stent implantation for left main coronary artery disease (from a two-center registry). *Am J Cardiol* 2010; 105: 343–351.

22 Park DW, Seung KB, Kim YH, *et al*. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. *J Am Coll Cardiol* 2010; 56: 117–124.

23 Ahn JM, Roh JH, Kim YH, *et al*. Randomized Trial of stents versus bypass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT study. *J Am Coll Cardiol* 2015; 65: 2198–2206.

24 Morice MC, Serruys PW, Kappetein AP, *et al*. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation* 2014; 129: 2388–2394.

25 Wu X, Chen Y, Liu H, *et al*. Comparison of long-term (4-year) outcomes of patients with unprotected left main coronary artery narrowing treated with drug-eluting stents versus coronary-artery bypass grafting. *Am J Cardiol* 2010; 105: 1728–1734.

26 Yi G, Youn YN, Hong S, *et al.* Midterm outcome of off-pump bypass procedures versus drug-eluting stent for unprotected left main coronary artery disease. *Ann Thorac Surg* 2012; 94: 15–22.

27 Yu XP, Wu CY, Ren XJ, *et al*. Very Long-term outcomes and predictors of percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting for patients with unprotected left main coronary artery disease. *Chin Med J (Engl)* 2016; 129: 763–770.

28 Zheng Z, Xu B, Zhang H, *et al*. Coronary artery bypass graft surgery and percutaneous coronary interventions in patients with unprotected left main coronary artery disease. *JACC Cardiovasc Interv* 2016; 9: 1102–1111.

29 Palmerini T, Benedetto U, Biondi-Zoccai G, *et al*. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2015; 65: 2496–2507.

30 Newman MF, Mathew JP, Grocott HP, *et al.* Central nervous system injury associated with cardiac surgery. *Lancet* 2006; 368: 694–703.

31 Tatoulis J, Buxton BF, Fuller JA. Patencies of 2127 arterial to coronary conduits over 15 years. *Ann Thorac Surg* 2004; 77: 93–101.

32 Zhang M, Guddeti RR, Matsuzawa Y, *et al*. Left internal mammary artery versus coronary stents: impact on downstream coronary stenoses and conduit patency. *J Am Heart Assoc* 2016; 5: e003568.
33 Bangalore S, Toklu B, Amoroso N, *et al*. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ* 2013; 347: f6625.
34 Ahn JM, Kang SJ, Yoon SH, *et al*. Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies. *Am J Cardiol* 2014; 113: 1338–1347.
35 De la Torre HJ, Baz AJ, Gomez HJ, *et al*. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. *JACC Cardiovasc Interv* 2014; 7: 244–254.
36 Fujino Y, Bezerra HG, Attizzani GF, *et al*. Frequency-domain optical coherence tomography assessment of unprotected left main coronary artery disease-a comparison with intravascular ultrasound. *Catheter Cardiovasc Interv* 2013; 82: e173–e183.

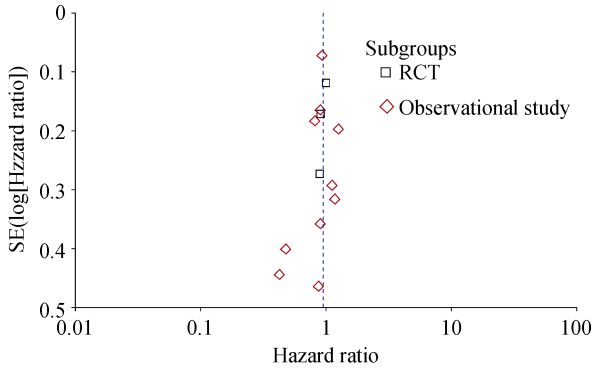

Figure 1S. Funnel plot of the composite of death, myocardial infarction or stroke. RCT: randomized controlled trial.

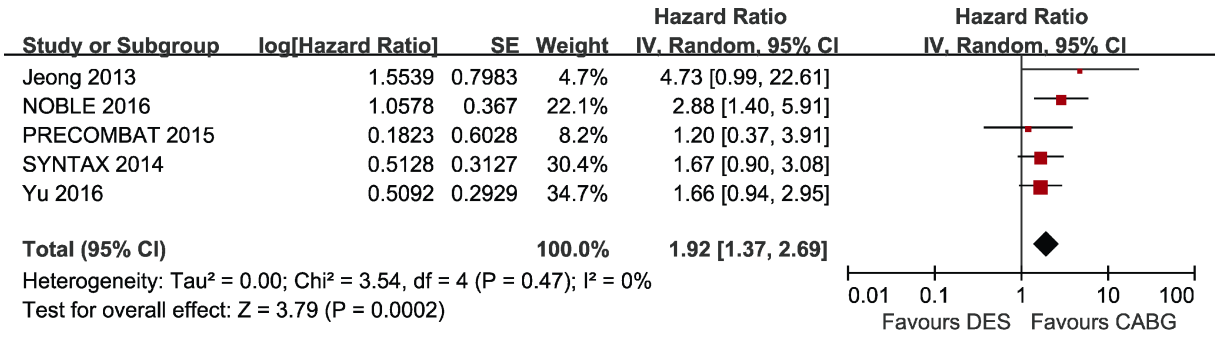

Figure 2S. Forest plot of myocardial infarction at ≥ 5-year follow up.

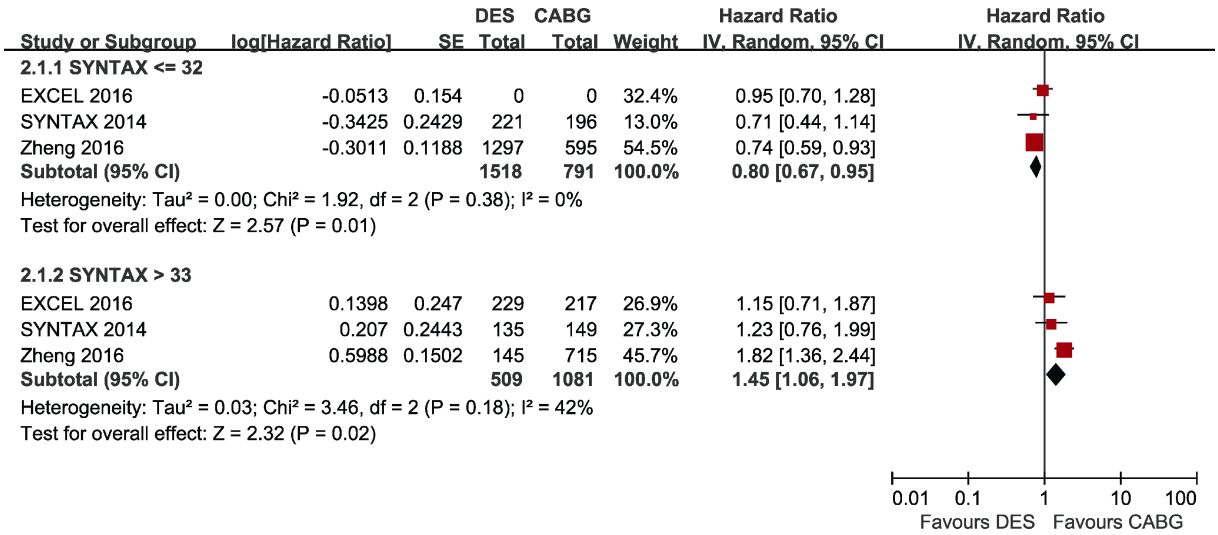

Figure 3S. Forest plot of the composite of death, myocardial infarction or stroke according to anatomic complexity (SYNTAX score ≤ 32 or > 32).

Table 1S. Definition of secondary outcomes.

Study	Definitions
ASAN-MAIN 2010	All deaths were considered cardiac unless an unequivocal noncardiac cause could be established. Q-wave MI was defined as the documentation of a new pathologic Q-wave after index treatment. TVR was defined as repeat revascularization of the treated vessel, including any segments of LAD or LCX. TLR was defined as any revascularization performed on the treated segment. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist on the basis of imaging studies.
Chang 2012	Death was defined as death from any cause. Q-wave MI was defined as documentation of a new abnormal Q wave after the index treatment. TVR was defined as repeat revascularization of the treated vessel, including any segments of LAD and LCX. Stroke, as indicated by neurological deficits, was confirmed by a neurologist on the basis of imaging studies.
Chieffo 2010	Deaths were classified as either cardiac or noncardiac. Cardiac death was defined as any death due to a cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), procedure-related deaths, and death of unknown cause. Non–Q-wave MI was defined as elevation of serum CK-MB isoenzyme that was 5 times the upper limit of normal (40 ng/mL) in the absence of pathological Q waves. Q-wave MI was defined as the development of new pathological Q waves in 2 or more contiguous leads with or without CK or CK-MB levels elevated above normal. Spontaneous MI was defined as the occurrence after hospital discharge of any value of troponin and/or CK-MB greater than the upper limit of normal if associated with clinical and/or electrocardiographic change. TLR was defined as any revascularization performed on the treated segment. TVR was defined as any reintervention performed on the treated vessel, considering also treatment of any segment in LAD and LCX. CVAs were defined as stroke, transient ischemic attacks, and reversible ischemic neurological deficits.
DELTA 2012	Deaths were classified as either cardiac or non-cardiac. Cardiac death was defined as any death due to a cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), procedure-related deaths, and death of unknown cause. Q-wave MI was defined as the development of new pathological Q waves in 2 or more contiguous leads with or without CK or CK-MB levels elevated above normal. Spontaneous MI was defined as the occurrence after hospital discharge of any value of troponin and/or CK-MB greater than the upper limit of normal if associated with clinical and/or electrocardiogram change. TLR was defined as any repeat intervention of the target lesion or other complication of the target lesion, defined as the treated segment 5 mm proximally to the stent and 5 mm distally to the stent. TVR was defined as any repeat intervention of any segment of the target vessel, defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself. CVAs were defined as stroke, transient ischemic attacks, and reversible ischemic neurological deficits.
EXCEL 2016	The cause of death will be adjudicated as being due to cardiovascular causes, non-cardiovascular causes, or undetermined causes. Cardiovascular death includes sudden cardiac death, death due to acute MI, heart failure or cardiogenic shock, stroke, other cardiovascular causes, or bleeding. Non-cardiovascular death is defined as any death with known cause not of cardiac or vascular causes. Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a noncardiovascular cause. For this trial all deaths of undetermined cause will be included in the cardiovascular category. Post procedure MI: Defined as the occurrence within 72 hours after either PCI or CABG of either: CK-MB >10x upper reference limit, or CK-MB >5x upper reference limit, plus new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related left bundle branch block, or angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Spontaneous MI: Defined as the occurrence >72 hours after any PCI or CABG of: the rise and/or fall of cardiac biomarkers (CK-MB or troponin) >1x upper reference limit, plus: ECG changes indicative of new ischemia [ST-segment elevation or depression, in the absence of other causes of ST-segment changes such as left ventricular hypertrophy or bundle branch block], or development of pathological Q waves ($\geq$ 0.04 s in duration and $\geq$1 mm in depth) in $\geq$2 contiguous precordial leads or $\geq$2 adjacent limb leads) of the ECG, or angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Table 1S. Cont.

Study	Definitions
EXCEL 2016	Strokes will be classified as ischemic, hemorrhagic, or unknown. Four criteria must be fulfilled to diagnosis stroke: (1) Rapid onset of a focal/global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia/aphasia, hemianopia, amaurosis fugax, other new neurological sign(s)/symptom(s) consistent with stroke; (2) duration of a focal/global neurological deficit ≥24 h or < 24 h if any of the following conditions exist: (i) at least one of the following therapeutic interventions: (a) pharmacologic (i.e., thrombolytic drug administration), (b) non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty); (ii) available brain imaging clearly documents a new hemorrhage or infarct; (iii) the neurological deficit results in death; (3) no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, other metabolic abnormality, peripheral lesion, or drug side effect). Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies; and (4) confirmation of the diagnosis by a neurology or neurosurgical specialist and at least one of the following: (a) brain imaging procedure (at least one of the following): (i) CT scan, (ii) MRI scan, (iii) cerebral vessel angiography; (b): lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) All strokes with stroke disability of modified Rankin Scale ≥1 (increase from baseline assessment) will be included in the primary endpoint. All diagnosed strokes (even with modified Rankin Scale 0) will also be tabulated. Ischemia-driven revascularization: A coronary revascularization procedure may be either a CABG or a PCI. The coronary segments revascularized will be sub-classified as: Target lesion: A lesion revascularized in the index procedure (or during a planned or provisional staged procedure). The LM target lesion extends from the left main stem ostium to the end of the 5 mm proximal segments of LAD and LCX as well as the ramus intermedius if the latter vessel has a vessel diameter of ≥ 2 mm. Target vessel: The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main and any vessel originating from the left main coronary artery or its major branches is, by definition, considered a target vessel for the purposes of this trial (unless either LAD or LCX are occluded at baseline and no attempt was made to revascularize these territories by either PCI or CABG). Target vessel non-target lesion: The target vessel non-target lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography. Non-target vessel: For the purposes of this trial, the only possible non-target vessel would be the right coronary artery and its major branches that were not treated by either PCI or CABG at the index procedure (unless either LAD or LCX are occluded at baseline and no attempt was made to revascularize these territories by either PCI or CABG).
Gao 2016	Death was defined as death from any cause. Nonfatal MI was defined as the occurrence after hospital discharge of any value of troponin and/or creatine kinase-myocardial band greater than the upper limit of normal if associated with clinical and/or electrocardiographic change. TVR was defined as any revascularization performed on a treated vessel. Stroke was indicated by neurological deficits adjudicated by a neurologist and confirmed by computed tomography scanning.
Jeong 2013	Death was defined as death from any cause. MI was defined as a CK-MB level >50 ng/ml or the appearance of new Q-waves or ST segment elevations >2 mm on the electrocardiogram. TVR was defined as any repeated revascularization performed on any treated vessel during the initial procedure using either OPCAB or PCI. Postoperative stroke was defined as a central neurological deficit persisting for >72 h, and was confirmed by CT or MRI.
Kang 2010	Death was classified as from either cardiac or noncardiac causes, according to the Academic Research Consortium definition. All deaths were considered cardiac in origin unless a noncardiac origin had definitely been documented. MI was defined according to the recommendations of the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force. TVR was defined as the repeat intervention (surgical or percutaneous) of any segment of the treated vessel, including the LM, LAD, and LCX. CVA, including both ischemic and hemorrhagic stroke.
MAIN-COMPARE 2010	Death was defined as death from any cause. Q-wave MI was defined as documentation of a new abnormal Q-wave after the index revascularization. TVR was defined as any repeat revascularization in any LAD or LCX as well as in the target segment. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist on the basis of imaging studies.

Table 1S. Cont.

Study	Definitions
NOBLE 2016	Death was defined as death from any cause. Cardiac death was defined as any death due to a suspected cardiac cause (MI, low–output heart failure, fatal arrhythmia), unwitnessed death and death of unknown cause. Non–procedure–related MI: A rise in biochemical markers exceeding the decision limit for MI (99th percentile including < 10% CV) with at least one of the following; (1) ischemic symptoms, (2) ECG changes indicative of ischemia (ST segment elevation or depression), and (3) development of a pathologic Q–wave with no relation to a PCI procedure. Repeat revascularisation: Any new PCI or CABG operation performed during follow–up. If an index revascularisation was attempted or successful, any subsequent revascularisation was counted as repeat revascularisation. TLR: Repeat revascularisation by PCI of any target segment treated during the index procedure. Stroke: Ischemic or haemorrhagic cerebrovascular event verified by brain CT or MRI.
PRECOMBAT 2015	Deaths were considered cardiac unless an unequivocal noncardiac cause was established. MI was defined as the appearance of new Q waves and an increase in the CK-MB concentration to more than 5 times the upper limit of the normal range, if occurring within 48 h after the procedure or as the appearance of new Q waves or an increase in the CK-MB concentration to greater than the upper limit of the normal range, plus ischemic symptoms or signs, if occurring more than 48 h after the procedure. TVR, in which repeat revascularization with either PCI or CABG was performed in the treated vessel, was considered to be driven by ischemia if the stenosis of any vessel was at least 50% of the vessel diameter in the presence of ischemic signs or symptoms or if the stenosis was at least 70% of the vessel diameter, even in the absence of ischemic signs or symptoms. Stroke was defined as a sudden onset of neurological deficit resulting from vascular lesions of the brain and persisting for more than 24 h.
SYNTAX 2014	Deaths were considered cardiac unless an unequivocal, noncardiac cause was established. MI was defined in relation to intervention status as follows i) after allocation but before treatment: Q-wave (new pathological Q-waves in ≥2 leads lasting ≥0.04 seconds with CK-MB levels elevated above normal), and non-Q wave MI (elevation of CK levels >2 times the upper limit of normal with positive CK-MB or elevation of CK levels to >2 times the upper limit of normal without new Q-waves if no baseline CK-MB was available); ii) <7d after intervention: new Q-waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5x the upper limit of normal; iii)≥7d after intervention: new Q waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5x the upper limit of normal or plasma level of CK 5x the upper limit of normal. Repeat revascularization was defined as any repeat PCI or CABG. CVA, or stroke was defined as a focal, central neurological deficit lasting >72 hours (h) which resulted in irreversible brain damage or body impairment.
Wu 2010	Death was defined as postprocedural death from any cause. Periprocedural MI (7 days after intervention) was defined as elevated serum CK-MB isoenzyme 5 times the upper limit of normal after CABG and 3 times the upper limit of normal after PCI. MI after the periprocedural period was defined as any typical increase and decrease of biochemical markers of myocardial necrosis with 1 of the following: cardiac symptoms, development of Q waves on electrocardiography, or electrocardiographic changes indicative of ischemia. TVR was defined as repeat revascularization of the treated coronary artery, including the corresponding segments of LAD and LCX. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist on the basis of imaging studies.
Yi 2012	MI was defined as CK-MB elevation with the appearance of new Q-wave or ST segment elevation greater than 2 mm on the electrocardiogram. TVR was defined as any repeated revascularization performed on any treated vessel during the initial procedure using either OPCAB or PCI.
Yu 2016	Cardiac death: Any death due to proximate cardiac cause (e.g., MI, low-output failure, and fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. Periprocedural MI (< 7 days after intervention) was defined as elevated serum CK-MB isoenzyme 5 times the upper limit of normal after CABG and 3 times the upper limit of normal after PCI. MI after the periprocedural period was defined as any typical increase and decrease of biochemical markers of myocardial necrosis with 1 of the following: cardiac symptoms, development of Q waves on electrocardiography, or electrocardiographic changes indicative of ischemia. Repeat revascularization included PCI and CABG. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist based on imaging studies.

Table 1S. Cont.

Study	Definitions
Zheng 2016	Death was defined as death from any cause. MI occurred when there were clinical signs and symptoms of ischemia that were distinct from the presenting ischemic event and meeting at least 1 of the following criteria: 1. Spontaneous (>48 h after PCI, and/or after CABG): A. New, significant Q waves in at least 2 contiguous leads of an ECG that were not present with the presenting ischemic event; B. Patients whose most recent cardiac markers measured before reinfarction, which were normal, require an increase in CK-MB or troponin above the 99th percentile limit of normal and at least ≥20% above the most recent value. 2. Within 48 h after PCI: A. Patients with normal biomarker values (preprocedure) who then develop an increase in biomarker values >5 times the 99th percentile upper reference limit or if the baseline values are elevated and are stable or falling, a rise of cTn values ≥20%. In addition, symptoms suggestive of myocardial ischemia or new ischemic electrocardiographic changes or angiographic findings consistent with a procedural complication or imaging demonstration of new loss of viable myocardium are required. B. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile upper reference limit. C. For patients with elevated baseline (preprocedure) cardiac biomarkers, there are 2 possible scenarios. In these scenarios, electrocardiographic changes or symptoms are not required to qualify. D. Patients with new, significant Q waves in at least 2 contiguous leads of an ECG that were not present with the presenting ischemic event. 3. Within 48 h after CABG: A CABG-related MI was defined by elevation of cardiac biomarker values >5 times the 99th percentile upper reference limit in patients with normal baseline cardiac troponin values (≤99th percentile upper reference limit) plus either new pathological Q waves; new left bundle-branch block, angiographically documented new graft, or native coronary artery occlusion; or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Repeat revascularization was defined as any repeat PCI or CABG. All stages of a staged index PCI procedure will be considered part of the index revascularization procedure and not a repeated revascularization. Stroke was defined as follows: 1. A focal neurologic deficit of central origin lasting >72 hours, or 2. A focal neurologic deficit of central origin lasting >24 hours, with imaging evidence of cerebral infarction or intracerebral hemorrhage, or 3. A nonfocal encephalopathy lasting >24 hours with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state, or Retinal arterial ischemia or hemorrhage is included in the definition of stroke.

ASAN-MAIN: ASAN medical center-left main revascularization; CABG: coronary artery bypass graft; CK-MB: creatine kinase-myocardial band; CT: computer tomography; CVA: cerebrovascular event; DELTA: drug-eluting stent for left main coronary artery disease; ECG: electrocardiogram; EXCEL: evaluation of Xience versus coronary artery bypass surgery for effectiveness of left main revascularization; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LM: left main; MI: myocardial infarction; MAIN-COMPARE: revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization study; MRI: magnetic resonance imaging; NOBAL: Nordic-Baltic-British left main revascularization; OPCABG: off-pump coronary artery bypass graft; PCI: percutaneous coronary intervention; PRECOMBAT: premier of randomized comparison of bypass surgery versus angioplasty using sirolimus-eluting stent in patients with left main coronary artery disease; SYNTAX: synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; TLR: target lesion revascularization; TVR: target vessel revascularization; ULMCA: unprotected left main coronary artery.

Table 2S. Assessment of randomized controlled trials.

Study	Sequence generation	Concealment of allocation	blinding of participants, personnel and outcome assessors	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
EXCEL 2016	Y	Y	N	Y	Y	Y
NOBLE 2016	Y	Y	N	Y	Y	Y
PRECOMBAT 2015	Y	Y	N	Y	Y	Y
SYNTAX 2014	Y	Y	N	Y	Y	Y

Table 3S. Assessment of observational studies.

Study	Selection	Comparability	Outcome	Total score
ASAN–MAIN 2010	4	2	3	9
Chang 2012	4	2	3	9
Chieffo 2010	3	2	1	6
DELTA 2012	4	2	3	9
Gao 2016	3	2	1	6
Jeong 2013	4	2	1	7
Kang 2010	4	2	2	8
MAIN-COMPARE 2010	4	2	3	9
Wu 2010	4	2	3	9
Yi 2012	3	2	3	8
Yu 2016	3	2	3	8
Zheng 2016	4	2	2	8